REMARKS

Status of the Claims

Claims 22 and 29 are amended and claims 36-39 are newly added. Support for the amendments is found generally throughout the specification and original claims, and specifically at p. 8, ll. 1-4. Accordingly, the amendments raise no issue of new matter. Claims 15 and 17-21 are canceled without prejudice. Applicants reserve the right prosecute canceled subject matter in related applications. Following entry of these claim amendments, claims 22, 24-29, and 31-39 are pending and under examination.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 15, 17-22, 24-29, and 31-35 stand rejected under 35 U.S.C. § 112, first paragraph for inadequate written description. This rejection is traversed by the present claim amendments and now may be withdrawn. Such action is respectfully requested.

Rejection Under 35 U.S.C. § 102

Claims 15, 17, 19, 20, 22, 24, 26, 28, 29, 31, 33, and 35 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Teimann (WO 01/11063). The Examiner alleges that Tiemann describes bicistronic viral vectors, identical to Applicants' vectors, for the treatment of malignant or metastatic cancers.

As currently amended, Applicants' claims encompass a method for treating p53-positive cancer cells using a bicistronic vector encoding both a p53 and p14ARF, wherein the p53- and p14ARF-encoding sequences are under the control of a single promoter. Tiemann does not teach or suggest treating p53-positive cancer cells using the disclosed vector construct. Tiemann provides only a single example of cells treated with both p53 and p14ARF. In this example, Hep3B cells are used. Tiemann at p. 16. These cells are well-known to be p53-negative (Bressac et al. Proc. Natl. Acad. Sci. USA, 87: 1973-1977, 1990; copy enclosed). Thus, at most, Tiemann

suggests the use of a p53/p14ARF biscistronic construct for treating p53-negative cancer cells; not p53-positive cancer cells as currently claimed by Applicants.

The invention as currently claimed is clearly novel over Tiemann, and the anticipation rejection may be withdrawn.

Rejection Under 35 U.S.C. § 103

All examined claims stand rejected as obvious over Roth et al. (U.S. Patent 5,747,469) in view of either or both of Lu et al. (Cancer Res. 62: 1305-1310, 2002) or Tango et al. (Hum. Gene Ther. 13: 1373-1382, 2002), Almond et al. (WO 99/47690), and Tiemann (WO 01/11063).

The Examiner alleges that Roth et al. disclose a variety of viral and non-viral vectors encoding p14ARF which are useful for treating cancer. The Examiner next alleges that both Lu et al. and Tango et al. disclose the treatment of p53-positive tumor cells with the co-transfection of p14ARF and p53 using separate viral vectors. The Examiner concludes that it would have been obvious to combine a p53 coding sequence (as disclosed in Lu et al. and Tango et al.) to the vectors of Roth et al., in a bicistronic construct. The Examiner alleges that Almond et al. provides a motivation to make such a bicistronic construct because such a construct would have reduced adverse effects (immunogenicity, oncogenicity, transduction efficiency) compared to the use of individual vectors. Finally, the Examiner further relies on the teachings of Tiemann which suggest the combination of p53 and p14ARF on a single vector construct.

The prior art provides neither a motivation to combine nor a reasonable expectation of success.

Applicants respectfully traverse this rejection. This rejection is based on the disclosures of Lu et al. and Tango et al. which show that simultaneous transfection of p53 and p14ARF are useful for inducing apoptosis in p53-positive cancer cells. However, the Examiner has erred in reasoning that the prior art motivates one to combine these constructs into a single bicistronic vector. Likewise, nothing in the prior art provides the artisan with a reasonable expectation of success.

The experiments described in both Lu et al. and Tango et al. use different amounts of the p53 and p14ARF vectors for infection. As such, they would not be amenable to combination into a single vector. Specifically, Lu et al. performs only a single experiment in which p53-positive cells are simultaneously infected with p53 and p14ARF. In this experiment, the A549 cells are infected with 100 pfu/cell of Ad-p53 and 40 pfu/cell Ad-ARF. See, Lu et al. at p. 1308, Figure 3. Likewise, Tango et al performs similar experiments using the p53-positive TE8 cells. In each of Tango's experiments, TE8 cells were infected with 5 moi Ad-p53 and either 10, 30, 50, or 100 moi of Ad-ARF. See, Tango et al. at p. 1376, Figure 2, and p. 1377, Figure 3B. The only instance in which Tango et al. used the same amount of p53 and p14ARF was in experiments using p53-negative cell lines (e.g., H358 cells; see Figure 5C).

When viewed together, it is clear that both Lu et al. and Tango et al. indicate that the levels of p53 and p14ARF infection should be regulated separately for the treatment of p53-positive cancer cells. Contrary to the Examiner's assertion, one would not be motivated to combine both coding sequences into a single bicistronic construct under the control of a single promoter for the treatment of p53-positive cancer cells, as required by Applicants' claimed method. Doing so makes it impossible to individually regulate the levels of the two proteins, as suggested by Lu et al. and Tango et al. Likewise, neither Lu et al nor Tango et al. provide a reasonable expectation that the use of the same amount of p53 and p14ARF (i.e., under the control of the same promoter) would be successful.

The teachings of Tiemann do not remedy these deficiencies in the combination of Lu et al. and Tango et al. As discussed above, Tiemann et al. provides no teachings with respect to p53-positive cancer cells. Tiemann's sole example involves Hep3B cells, which are p53-negative. Thus, Tiemann cannot provide either a motivation to combine or a reasonable expectation of success.

Almond et al. also fails to remedy the deficiencies of this rejection. Although Almond et al. may provide teachings on the general advantages of making bicistronic constructs, it does not specifically address the deficiencies raised here by the combination of Lu et al. and Tango et al.

The teachings of Roth et al. are of little import here. Nothing in Roth et al. is directed to the use of a bicistronic construct, let alone one encoding both p53 and p14ARF under the control of a single promoter. Thus, Roth et al. cannot provide the motivation to combine or the reasonable expectation of success necessary to sustain this obviousness rejection.

When taken together, the prior art relied upon by the Examiner fails to provide the artisan with a motivation to combine p53 and p14ARF into a bicistronic vector, under the control of a single promoter, for the treatment of p53-positive cancer cells. The art clearly demonstrates a perceived need for independent regulation of the infective levels of each construct, thus negating the possibility of their combination into a single vector. Likewise, because the prior art consistently used different levels of each expression vector for p53-positive cancers, there is no expectation that their combination into a single vector would be successful in achieving the same result. Thus, the Examiner has failed to make a *prima facie* case of obviousness and, for this reason alone, the rejection is traversed and should be withdrawn.

Applicants demonstrate surprising and unexpected results using the bicistronic construct for the treatment of p53-positive cancer cells.

Even accepting, *arguendo*, that a *prima facie* case of obviousness has been made, it may be rebutted by evidence of an unexpected result. M.P.E.P. § 2144.08(II)(B) ("Rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art.").

Applicants first demonstrate that the p53/p14ARF bicistronic construct possesses several surprising and unexpected properties for the treatment of p53-positive cancer cells. In Figure 3A, Applicants demonstrate that the p53/p14ARF bicistronic construct is effective *in vitro* at killing N2O2 cells; a p53-positive cancer cell line. This would not necessarily have been predicted by the findings of Lu et al. and Tango et al. which both used individualized amounts of the two constructs in order to effect cell killing.

Applicants also demonstrate that the p53/p14ARF bicistronic construct effects p53-positive cell killing *in vivo*. The Examiner's attention is respectfully drawn to Figure 5 of the Specification and Figure 3 of Huang et al. (Cancer Res. 63: 3646-3653, 2003; copy enclosed). Huang et al. is a post-filing scientific publication by the inventors disclosing and expanding upon the data present in the specification. As shown in the identified figures, N2O2 cells were implanted subcutaneously into nude mice. The resulting tumors were subsequently periodically injected with either the bicistronic construct, a vector containing only p53, or a control vector. In the experiment shown in Figure 5 of the specification, the bicistronic construct induced growth arrest of the tumor over the 15 day study period demonstrated by a stabilization in tumor volume. In the experiment shown in Figure 3 of Huang et al., the bicistronic construct effectively eliminated the tumor which was demonstrated histologically. By contrast, similar treatment with a p53 vector was merely able to induce growth arrest, resulting in no change in the net number of tumor cells observed.

Finally, Applicants demonstrate, in Figure 3B and 3C of the Specification, that the bicistronic construct provides a significantly enhanced cancer cell killing compared to the simultaneous use of p53 and p14ARF on individual vectors. Although this result was obtained in a p53-negative tumor cell line, it further demonstrates the surprising and unexpected properties inherent in Applicants' bicistronic construct.

In sum, Applicants clearly demonstrate unexpected and superior results in the treatment of cancer cells using of a bicistronic construct comprising p53 and p14ARF, wherein both coding sequences were under the control of a single promoter. Accordingly, even if a *prima facie* case of obviousness has been made (which it has not), the rejection is traversed by the unexpected results provided in the specification. For the foregoing reasons, Applicants submit that the presently claimed invention is unobvious and that this rejection should be withdrawn.

Double Patenting

The Examiner continues to object to claims 29 and 31-35 as substantial duplicates of claims 22 and 24-28. As such, the Examiner alleges that claims 29 and 31-35 would be rejected for duplicate claiming should claims 22-28 be found allowable. The Examiner alleges that there is no material or procedural difference evident between the methods and that merely reciting different outcomes does not impart a different claim scope. Applicants respectfully disagree.

Applicants respectfully direct the Examiner's to Figure 5 of the Specification and Figure 3C of Huang et al. Both experiments involve the *in vivo* treatment of N2O2 cells transplanted subcutaneously into nude mice. However, the treatment regimen used for the experiments in Figure 5 of the Specification resulted in a mere growth arrest of the tumor (i.e., tumoristatic), as evidence by no significant net change in tumor volume. By contrast, the conditions used in the experiments detailed in Figure 3 of Huang et al. clearly resulted in a tumoricidal effect.

Thus, Applicants have provided actual data demonstrating that, depending upon the specific treatment regimen, growth arrest or cell killing/apoptosis can be induced. This data clearly supports Applicants' assertion that claims 22 and 24-28 are not coextensive with claims 29 and 31-35. Accordingly, this double patenting rejection is improper and should be withdrawn.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to

Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741

Respectfully submitted,

Date 8/13/07

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Enclosures—Bressac et al. (*Proc. Natl. Acad. Sci. USA*, Vol. 87, 1973-1977, March 1990)
Huang et al. (Cancer Research, Vol. 63, 3646-3653, July 1, 2003)